REMARKS

Claims 1-3 and 5-22 are pending in the present application. Claim 4 has been withdrawn from consideration subsequent to a restriction requirement. Claims 1, 5 and 14 have been amended. New claims 21-22 have been added. Support for new claim 21 can be found on page 8 of the application. Support for new claim 22 can be found on page 14. No new matter has been added.

In the Action, the Examiner objected to claim 5 because the term "manosidase" is a misspelling. Claim 5 has been amended to delete "manosidase".

In the Action, the Examiner also rejects claim 5 under 35 USC § 112, ¶2, noting that decarboxylase, glucokinase, and hexokinase are not hydrolases as required by claim 1, and therefore lack antecedent basis. The Examiner also notes that guanidinobenzodase does not appear to be the art accepted name of any known enzyme and that an EC for glutathionase could not be found. Applicant has amended claim 5 to delete the reference to decarboxylase, glucokinase, hexokinase, guanidinobenzodase, and glutathionase. Withdrawal of this rejection is respectfully requested.

Claim Rejection under 35 U.S.C. § 102

The Action rejects claims 1, 5-15 and 17-20 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,851,527 to Hansen. This ground of rejection is respectfully traversed.

Claim 1 has been amended to recite a method for the in-vivo localization of water-insoluble molecules within a solid tumor comprising the administration of a water-soluble prodrug molecule to an animal, "said prodrug being a substrate to said enzyme and hydrolyzed by said enzyme molecules present within the tumor, said hydrolysis forming a water insoluble drug precipitate molecule, wherein said precipitate is trapped within the extracellular space of the solid tumor.

Hansen discloses injecting a mammal with an enzyme-antibody conjugate and thereafter injecting the mammal with a soluble substrate-agent conjugate which is capable of

transformation by the enzyme to form product comprising the agent, which accumulates at the target site for treatment and/or diagnosis. Hansen does not teach or suggest that a precipitate is trapped within the extracellular space of a solid tumor as required by claim 1. Rather, Hansen teaches that "[t]he enzyme can transform many molecules or subunits of substrate-agent conjugate to liberate many molecules of product in a form which will accrete at the target site due to favorable partition between the fluid bathing the target site and the tissue or other antigen-containing medium at the site itself" (column 3, lines 47-53). Hansen also states that the substrate-agent conjugate "must also be capable of reaching the target and being transformed to a product which has a substantially more favorable partition coefficient for attraction to the site than the conjugate" (column 6, lines 62-66). Hansen further states that "[t]he free drug would then be rendered significantly less soluble in the interstitial fluid, and would tend to deposit on the cell membrane of surrounding cells and exert its cytotoxic effect at the site of localization of the antibody-enzyme conjugate" (column 7, lines 50-54) and "[t]he agent molecules are bound to the polymer in such a way that cleavage by the enzyme will liberate the agent, free of polymer units or bound to a small enough number of units to have the requisite lower solubility, or more favorable partition coefficient to cells, tissues, lesion, lesion components or the like loci at the target site, relative to the fluid bathing such loci" (column 8, lines 18-24). Each of these statements states or suggests that the cleaved drug product is in some way deposited on, or potentially even permeates into, the cells of the tumor, and thus would not be trapped within the extracellular space of a solid tumor as required by claim 1. Therefore claim 1 should be allowable over the Hansen reference. As claims 2-3 and 5-22 depend from claim 1, they should be allowable for the same reason.

The Action rejects claims 1, 5-15 and 20 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,361,774 to Griffiths et al. This ground of rejection is respectfully traversed.

Griffiths et al. disclose pretargeting an enzyme to a mammalian target site and administering a cytotoxic drug in an initially detoxified prodrug form, which is converted to the more toxic drug in situ by the enzyme. Griffiths et al. do not teach or suggest that a precipitate is trapped within the extracellular space of a solid tumor as required by claim 1. Rather, Griffiths

et al. disclose a method for increasing the target-specific toxicity of a chemotherapy drug (column 2, lines 1-7), and also that the targeted enzyme will regenerate the drug to amplify its target-specific activity (column 8, lines 8-10). As with the Hansen reference, these statements suggest that the regenerated drug targets the cell and thus would not be a precipitate that is trapped within the extracellular space of a solid tumor. Unlike the drugs described in the Hansen and Griffiths et al. references, the drugs described in the present application are not chemotherapeutic and do not target or act directly upon any cell component. For these reasons, claim 1 should be allowable over Griffiths et al. As claims 5-15 and 20-22 depend from claim 1, they should be allowable for the same reason.

Claim Rejection under 35 U.S.C. § 103

The Action rejects claims 1-3 and 5-20 under 35 U.S.C. 103(a) as being unpatentable over Hansen in view of U.S. Patent No. 4,975,278 to Senter et al., U.S. Patent No. 6,495,553 to Shepard and further in view of U.S. Patent No. 6,265,427 to Camden, U.S. Patent No. 6,156,739 to Griffen et al., and U.S. Patent No. 5,854,968 to Horwitz et al. This ground of rejection is respectfully traversed.

Senter et al. fails to cure the deficiency of Hansen with respect to the limitation of a precipitate being trapped within the extracellular space of a solid tumor as required by claim 1. Senter et al. discloses a method for delivering cytotoxic drugs to tumor cells by the administration of a tumor-specific antibody-enzyme conjugate and the additional administration of a prodrug this is converted at the tumor site, in the presence of the antibody-bound enzyme, to an active cytotoxic drug. Senter et al. states that the "drug is . . .activated extracellularly and can diffuse into all of the tumor cells at that site". Thus, Senter et al. cannot teach or suggest water-insoluble drug precipitate molecule, wherein said precipitate is trapped within the extracellular space of the solid tumor.

Shepard also fails to cure the deficiency of Hansen with respect to the limitation of a precipitate being trapped within the extracellular space of a solid tumor as required by claim 1. Shepard discloses methods and examples of molecules for selectively killing a pathological cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular

enzyme. The prodrug is subsequently converted to a cellular toxin. As with the previous references, Shepard deals with chemotherapeutic agents which are necessarily internalized into the cell and directly act upon a cell component. Thus, Shepard does not teach or suggest a drug which precipitates and is trapped within the extracellular space of a solid tumor.

Camden also fails to cure the deficiency of Hansen with respect to the limitation of a precipitate being trapped within the extracellular space of a solid tumor as required by claim 1. Camden discloses a method of treating leukemia using a specific compound or a prodrug form of such compound. Camden does not teach or suggest that such compound precipitates and is trapped within the extracellular space of a solid tumor.

Griffin et al. disclose phosphate derivatives of quinazolinone compounds useful as prodrugs for providing active PARP inhibiting substances for medical use in conjunction with a cytotoxic drug or radiotherapy. There is no teaching or suggestion of a water-insoluble drug precipitate molecule, wherein the precipitate is trapped within the extracellular space of a solid tumor. Rather Griffin et al. suggest a quinazolinone compound having greater aqueous solubility and that such compound may be effective in interfering with intracellular DNA repair mechanisms.

Horwitz et al. disclose a process for producing substantially impurity-free Bi-213 cations. There is no teaching or suggestion whatsoever of a water-insoluble drug precipitate molecule, wherein the precipitate is trapped within the extracellular space of a solid tumor. And therefore, Horwitz et al. likewise fails to cure the deficiency of Hansen with respect to this limitation of claim 1.

Thus, as no cited reference, whether singly or in combination, teaches or suggests "a water-insoluble drug precipitate molecule, wherein said precipitate is trapped within the extracellular space of the solid tumor, claim 1 should be allowable over these references. As claims 2-3 and 5-22 depend from claim 1, they should be allowable for the same reason.

In view of the foregoing remarks and amendments, Applicant submits that this application is in condition for allowance at an early date, which action is earnestly solicited.

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The Assistant Commissioner for Patents is hereby authorized to charge any additional fees or credit any excess payment that may be associated with this communication to deposit account **04-1769**.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please enter the following complete set of claims. A marked up version of the claims showing changes made appears after the remarks.

1. (Amended) A method for the enzyme-mediated, site-specific, in-vivo localization of water-insoluble molecules within a solid tumor, which comprises:

the administration of a water-soluble prodrug molecule to an animal;

said prodrug being a substrate to said enzyme and hydrolyzed by said enzyme molecules present within the tumor, said hydrolysis forming a water-insoluble drug precipitate molecule, wherein said precipitate is trapped within the extracellular space of the solid tumor.

2. (Unchanged) The method as recited in claim 1, wherein the enzyme is produced naturally by tumor cells.

3. (Unchanged) The method as recited in claim 2, wherein the enzyme is produced at concentrations higher than that in normal tissues.

Claim 4 is withdrawn from consideration.

5. The method as recited in claim 1, wherein the enzyme is selected from the group consisting of a phosphatase, a cellulase, a deaminase, [a decarboxylase,] a DNAse, an endonuclease, an exonuclease, [a glucokinase,] a glucosidase, a glutaminase, [glutathionase, a guanidinobenzodase,] a glucoronidase, [a hexokinase,] an iduronidase, [a manosidase,] a nitrophenylphosphatase, a peptidase, a protease, an RNAse, and a sulfatase.

6. (Unchanged) The method as recited in claim 1, wherein the enzyme is localized specifically on the surfaces of tumor cells, following the administration of said enzyme chemically conjugated to a targeting moiety.

7. (Unchanged) The method as recited in claim 6, wherein the targeting moiety is a ligand that binds specifically to a tumor-specific receptor.

8. (Unchanged) The method as recited in claim 7, wherein the ligand is selected from the group consisting of an antibody, a peptide, and a hormone.

9. (Unchanged) The method as recited in claim 8, wherein the receptor is a tumor-specific antigen.

10. (Unchanged) The method as recited in claim 8, wherein the receptor is specific to the peptide.

11. (Unchanged) The method as recited in claim 8, wherein the receptor is specific to the hormone.

12. (Unchanged) The method as recited in claim 6, wherein the conjugate is injected intravenously, intra-arterially, subcutaneously, into the lymphatic circulation, intraperitoneally, intrathecally, intratumorally, or intravesically.

13. (Unchanged) The method as recited in claim 1, wherein the water-soluble prodrug is injected intravenously, intra-arterially, subcutaneously, into the lymphatic circulation, intraperitoneally, intrathecally, intratumorally, intravesically, or is given orally.

14. (Amended) The method as recited in claim 1, wherein the prodrug substrate is represented by the following formula:

$R[^{1}]$–D–(O–BLOCK)

wherein BLOCK is a blocking group that can be cleaved from the remainder of the substrate by action of an enzyme, resulting in a water-insoluble drug molecule represented by the following formula:

$R[^{1}]$–D–O–H

wherein D contains a minimum of 2 linked aromatic rings, and $R[^{1}]$ is a radioactive atom, a radiolabeled moiety with one or more radioactive atom(s), a boron atom, or a moiety labeled with one or more boron atoms.

15. (Unchanged) The method as recited in claim 14, wherein the radiolabel is selected from the group consisting of a gamma emitting radionuclide suitable for gamma camera imaging, a positron emitting radionuclide suitable for positron emission tomography, and an alpha or a beta particle emitting radionuclide suitable for therapy.

16. (Unchanged) The method as recited in claim 15, wherein the alpha particle emitting radionuclide is astatine-211, bismuth-212, or bismuth-213.

17. (Unchanged) The method as recited in claim 15, wherein the beta particle emitting radionuclide emits beta particles whose energies are greater than 1 keV.

18. (Unchanged) The method as recited in claim 15, wherein the beta particle emitting radionuclide is iodine-131, copper-67, samarium-153, gold-198, palladium-109, rhenium-186, rhenium-188, dysprosium-165, strontium-89, phosphorous-32, phosphorous-33, or yttrium-90.

19. (Unchanged) The method as recited in claim 14, wherein the boron atom is suitable for neutron activation.

20. (Unchanged) The method as recited in claim 14, wherein the BLOCK is selected from the group consisting of:

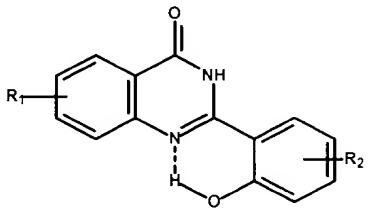
a monovalent blocking group derivable by removal of one hydroxyl from a phosphoric acid group, a sulfuric acid group, or a biologically compatible salt thereof;

a monovalent blocking group derivable by removal of a hydroxyl from an alcohol or an aliphatic carboxyl, an aromatic carboxyl, an amino acid carboxyl, or a peptide carboxyl; and

a monovalent glycoside derived by the removal of the anomeric hydroxyl group from a mono- or polysaccharide.

Please add the following new claims:

21. (New) The method of claim 14, wherein R-D comprises quinazolinone dye having the formula:



wherein R comprises R_1 and/or R_2 and R_1 and R_2 comprise a radioactive atom, a radiolabeled moiety with one or more radioactive atom(s), a boron atom, or a moiety labeled with one or more boron atoms.

22. (New) The method of claim 14, wherein R-D comprises a the following compound resulting from the enzymatic hydrolysis of 5-bromo-4-chloro-3-indolyl β –D-galactose by β - D-galactosidase: